Original Article

Anti-thyroid peroxidase antibody positivity during early pregnancy is associated with pregnancy complications and maternal morbidity in later life

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Abstract

Aims: We assessed the impact of detecting anti-thyroid peroxidase antibodies (anti-TPO-Ab) in the first trimester of pregnancy on pregnancy outcomes and maternal thyroid function during the postpartum period. **Materials and Methods:** In a prospective study consisting 400 pregnant women (8-12 weeks pregnant) were screened for their thyroid profile and followed-up to 12 weeks postpartum. Patients with abnormal thyroid function at 12 weeks postpartum were further followed-up with repeated assessment of thyroid stimulating hormone (TSH) and serum-free thyroxine-4 levels at 8 weeks interval up to 12 months postpartum. **Results:** 11.5% of the subjects were positive for anti-TPO-Ab who had mean TSH level of 2.31 μIU/ml, which was significantly (*P*- 0.0001) higher than pregnant women negative for anti-TPO-Ab (1.73 μIU/ml). Increased incidence of miscarriage was observed in anti-TPO positive mothers when compared to antibody negative mothers. Postpartum thyroid dysfunction developed in 4.7% cases at 12 weeks, among them antibody positivity was observed in 81.25% of subjects. In 18.75% mothers positive for anti-TPO-Ab, the thyroid dysfunction persisted up to 12 months postpartum. **Conclusions:** Thyroid antibodies detected in early pregnancy seems to be predicting pregnancy complications and later maternal thyroid disease related morbidity.

Key words: Outpatient department, postpartum thyroid dysfunction, postpartum thyroiditis, thyroid peroxidase antibody

INTRODUCTION

Thyroid peroxidase (TPO), is a membrane-bound enzyme, which catalyzes iodide oxidation and iodination of tyrosyl residues of thyroglobulin.[1-3] Anti-TPO-antibody (anti-TPO-Ab) can react with TPO, leading to the destruction of thyrocytes. Autoantibodies to TPO are common in the euthyroid population and are associated with major alterations in the course of pregnancy affecting the mother, fetus, and/or neonate. Although the presence of TPO-Ab is associated with increased rate of pregnancy complications such as miscarriage, placental abruption, pregnancy-induced hypertension, and preterm delivery,[4] these relationships are not proved in all studies. Women with high antibody titer in early pregnancy are commonly affected with postpartum thyroid dysfunction (PPTD)[5] with its potential impact on future pregnancies.

We conducted this study in tertiary care hospital to evaluate the incidence of TPO-Ab positivity in women attending antenatal outpatient department (OPD), to determine the effects of presence of thyroid antibody (anti-TPO-Ab) in antenatal period on pregnancy outcomes, the incidence of PPTD and its natural course.

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MATERIALS AND METHODS

The present study was undertaken in a tertiary care institute from April 2011 to October 2012, where consecutive 400 pregnant women from booked antenatal cases were screened. The study was approved by Institute's Ethics Committee following which subjects were enrolled after adequate informed consent was obtained. In this prospective cohort study, mothers with a singleton pregnancy without any sorts of known previous thyroid disorder were included. Mothers with pregnancy in congenitally malformed uterus, fibroid uterus, known cervical incompetence, and history of smoking were excluded.

Serum Free T_4, Free T_3, and thyroid-stimulating hormone (TSH) and serum anti-TPO-Ab levels were measured routinely in their first antenatal visit (median gestational age at sampling was 10 weeks). Thorough and detailed history of each case was recorded. Special importance were given to detailed obstetric history; medical history of autoimmune diseases, diabetes, previous history of miscarriage, family history of diabetes, autoimmune thyroid diseases, and other autoimmune diseases. They were closely monitored in the antenatal clinic and the labor ward following admission. All subjects were followed-up in OPD during routine postnatal visit. Serum Free T_4 and TSH levels were repeated in all cases routinely at 12 weeks after delivery. All subjects with abnormal thyroid function at 12 weeks postpartum were followed-up with repeated serum Free T_4 and TSH levels at 8 weeks interval up to 12 months postpartum (telephonic contact was maintained). During follow-up visits, complaints are noted carefully with special reference to signs of thyroid diseases. Endocrinology consultations were also done.

Normal reference range in pregnancy (as per our hospital reference value)

Thyroid-stimulating hormone: 0.35-2.5 μIU/ml; Free T_3: 2.3-4.2 pg/dl; Free T_4: 0.89-1.7 ng/dl

Postpartum hypothyroidism may be defined as either a serum TSH concentration >3.6 μIU/ml together with a free T_4 <0.6 ng/dl or a TSH ≥10 μIU/ml

Assay methods

Serum Free T_4, Free T_3, and TSH level were measured by ELISA; serum anti-TPO-Ab levels were measured by chemiluminescence.

Statistical analysis was performed by Graphpad prism software(GraphPad Software, Inc. San Diego, CA 92130; USA). All the data are normally distributed. Categorical variables were compared between groups by Chi-square test; numerical variables were compared by Student's *t*-test. All analyses were two-tailed and $P < 0.05$ was considered to be statistically significant.

RESULTS

Of the 400 antenatal mothers screened for thyroid status, the postpartum follow-up records were incomplete in 38 cases, and these were excluded from the study [Figure 1].

Of 400 antenatal mothers, 46 detected positive for anti-TPO-Ab, giving an incidence rate of 11.5%. The incidence of subclinical hypothyroidism in mothers attending our antenatal clinic was 5.25% (21 out of 400). The percentage of anti-TPO-Ab positivity in euthyroid mothers was 11.34% (43 out of 379) and the percentage of anti-TPO-Ab positivity in cases of subclinical hypothyroid antenatal mothers was 14.28% (3 out of 21).

Totally, 41 mothers (9 TPO-Ab positive and 32 TPO-Ab negative) with TSH level of >2.5 μIU/ml received Levothyroxine therapy. It was started at a dose of 25 mcg/day as per endocrinologist recommendation and the final dose was titrated according to next thyroid profile. It was noted that the average dose of Levothyroxine required was significantly higher in TPO-Ab positive patients [Table 1].

About 38.24% anti-TPO-Ab positive mothers were <25 years age group. Antibody positivity was observed in 2.17% (1 out of 46) of women, which was associated with autoimmune medical disorder.

Mean serum TSH level was significantly ($P < 0.0001$) higher (2.31 vs. 1.73 μIU/ml) among TPO-Ab positive than negative mothers. Increased incidence of past history miscarriage was observed in TPO-Ab positive mothers than in antibody negative mothers [Table 1].

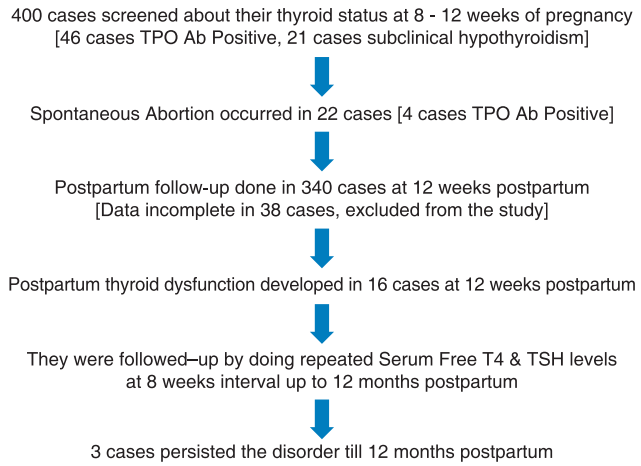

Figure 1: Consort diagram

In our study, 10.87% of anti-TPO-Ab positive mothers had a spontaneous abortion and in case of anti-TPO-Ab negative mothers, it was 4.8%, however, this difference was not statistically significant ($P = 0.16$) [Table 2]. Again 14.28% of anti-TPO-Ab positive mothers had preterm delivery and in case of anti-TPO-Ab negative mothers, it was 8.6% ($P = 0.496$) [Table 2].

Postpartum thyroid dysfunction developed in 16 cases (incidence of 4.7%). Among them, antibody positivity was observed in 81.25% subjects [Table 3]. Of 16 mothers who were found to have PPTD at 12 weeks, 3 mothers persisted the disorder up to 12 months postpartum. During the course of PPTD, hypothyroidism was observed in 31.23% (5 out of 16), hyperthyroidism alone observed in 25% (4 out of 16) and hyperthyroidism followed by subclinical hypothyroidism was observed in 43.75% (7 out of 16) of cases. Average duration of PPTD was about 7 months. Symptoms present at the time of detection of PPTD were vague and nonspecific (fatigue, irritability, lethargy, etc.). 6.25% (1 out of 16) women develop a small painless goiter. 18.75% (3 out of 16) of cases who developed PPTD required Levothyroxine therapy.

DISCUSSION

The presence of thyroid autoantibodies is nonspecific, being present in up to 20% of biochemically euthyroid pregnant women.[6-8] However, 10% of normal adults have high serum anti-TPO-Ab concentrations, and the prevalence increases up to 30% among elderly.[9] In our study, the percentage of anti-TPO-Ab positivity in mothers attending antenatal clinic was 11.5%.

Table 1: Baseline characteristics of mothers analyzed during pregnancy

Characteristics	TPO-Ab positive (*n* = 46)	TPO-Ab negative (*n* = 354)	*P*
Age (mean) years	25.06	24.45	0.3158
Parity (mean)	0.82	0.55	0.0003
TSH level (mean) μIU/ml	2.31	1.73	0.0001
Levothyroxine required (mean) μg/day	47.22	34.37	0.0354
Past history of miscarriage *n* (%)	6 (13.04)	20 (5.64)	0.1012
Past history of preterm delivery *n* (%)	4 (8.69)	19 (5.36)	0.3206
Past history of preeclampsia *n* (%)	5 (10.86)	22 (6.21)	0.2190
	1 (2.17)	0	0.1150

TPO-Ab: Thyroid peroxidase antibody, TSH: Thyroid stimulating hormone

Table 2: Pregnancy complications in respect to TPO-Ab status

Characteristics	TPO-Ab positive	TPO-Ab negative	*P*
Miscarriage *n* (%)	5 out of 46 (10.87)	17 out of 354 (4.8)	0.1573
Preeclampsia *n* (%)	7 out of 42 (16.66)	31 out of 337 (9.19)	0.1668
Preterm delivery *n* (%)	6 out of 42 (14.28)	29 out of 337 (8.6)	0.2541
Placental abruption *n* (%)	1 out of 42 (2.38)	2 out of 337 (0.59)	0.2977
NICU admission *n* (%)	3 out of 42 (7.14)	11 out of 337 (3.26)	0.1941

TPO-Ab: Thyroid peroxidase antibody, NICU: Neonatal intensive care unit

In a previous survey of pregnant women, 2% had subclinical hypothyroidism and 58% of had high anti-TPO-Ab concentration.[10] While in our study, only 14.28% had high anti-TPO-Ab concentration. This may be due to the iodine deficiency which is the most common cause of hypothyroidism in our country in comparison to autoimmune thyroid disorders.[11]

It is noted that the thyroid antibody titers remain very low with the TSH level >2 μIU/L. The titer rises with the TSH level beyond 2 μIU/L or higher.[3] In our study, TSH level in majority of TPO-Ab positive cases was 2 μIU/ml, which was significantly different (*P*-0.001) between TPO-Ab (+) ve and (–)ve groups [Table 1].

The association between thyroid autoimmunity and increased fetal loss is previously reported.[7,12] In our study as well, although not statistically significant ($P = 0.16$), anti-TPO-Ab positive mothers had a higher spontaneous abortion rate than anti-TPO-Ab negative mothers (10.87% vs. 4.8%, respectively). TPO-Ab-positive women had a significant increase in preterm delivery compared with antibody-negative women (26.8 vs. 8.0%, $P = 0.01$),[13] which is consistent with our observation (14.28 vs. 8.6% respectively).

The biphasic biochemical pattern (initial thyrotoxicosis due to an excessive release of preformed thyroid hormone, followed by hypothyroidism) is observed in almost 90% of patients,[14-16] while a variable incidence from 3% to 17% is reported worldwide.[17,18] Women with thyroid antibodies in the first trimester have a 33-50% chance of having postpartum thyroiditis (PPT).[19,20] Regarding the incidence of PPTD, the result of our study (4.7%) is lower than previous reports, which may be because we had screened all the subjects only once (at 12 weeks postpartum) and hence could have missed the cases who may have developed PPTD in later weeks of postpartum period. In our study, significantly ($P = 0.0001$) higher number of the antibody-positive mother (30.95% vs. 1.006%) developed PPTD [Table 3].

Quantitative evaluation of depressive symptomatology shows an increase of mild to moderate depression in thyroid antibody positive women even when they remain euthyroid during the postpartum period.[21] Several studies from different countries have shown that about 12-61% of women who develop postpartum hypothyroidism become chronically hypothyroid.[22,23] In those women who do not develop permanent hypothyroidism, the chance of experiencing a recurrence of PPTD after a previous episode is around 70%.[24] In this study, 18.75% mothers persisted the disorder up to 12 months postpartum.

Table 3: Development of PPTD in respect to TPO-Ab status

TPO-Ab positive cases (*n* = 42)		TPO-Ab negative cases (*n* = 298)		*P*
Developed PPTD	Not developed PPTD	Developed PPTD	Not developed PPTD	
13	29	3	295	0.0001

PPTD: Postpartum thyroid dysfunction, TPO-Ab: Thyroid peroxidase antibody

The main limitation in our study is the time of recruiting participants at 8-12 weeks of gestation (median 10 weeks), as most abortions or pregnancy loss occur before 8th week of gestation.

Despite the controversy around screening for postpartum thyroiditis measurement of serum soluble CD4 concentration drawn in the 1st month postpartum may prove an ideal test for population screening for impending PPT.[25] Long-term follow-up of women who had an episode of PPT reveals a 20-40% incidence of permanent primary hypothyroidism. Identifying the women at increased risk for developing permanent hypothyroidism[26] will help in its prevention and better clinical management. Moreover, the test for anti-TPO-Ab is cheap and not associated with any ethical issues. A recent review of selenium concluded that selenium administration is effective in decreasing the TPO-Ab titer, incidence of PPT, and permanent hypothyroidism.[27] Nevertheless, treatment of TPO-Ab positive women with selenium to prevent PPT remains premature.

CONCLUSION

Thyroid antibodies detected in early pregnancy seem to predict pregnancy complications and later thyroid disease morbidity of the mother. Hence, screening should include an anti-TPO-Ab titer and TSH level, as the presence of antibody identifies women with much increased risk of developing pregnancy complications and postpartum thyroiditis.

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